The impact of a massive transfusion protocol (1:1:1) on major hepatic injuries: Does it increase abdominal wall closure rates?

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Background: Massive transfusion protocols (MTPs) using high plasma and platelet ratios for exsanguinating trauma patients are increasingly popular. Major liver injuries often require massive resuscitations and immediate hemorrhage control. Current published literature describes outcomes among patients with mixed patterns of injury. We sought to identify the effects of an MTP on patients with major liver trauma.

Methods: Patients with grade 3, 4 or 5 liver injuries who required a massive blood component transfusion were analyzed. We compared patients with high plasma:red blood cell:platelet ratio (1:1:1) transfusions (2007–2009) with patients injured before the creation of an institutional MTP (2005–2007).

Results: Among 60 patients with major hepatic injuries, 35 (58%) underwent resuscitation after the implementation of an MTP. Patient and injury characteristics were similar between cohorts. Implementation of the MTP significantly improved plasma: red blood cell:platelet ratios and decreased crystalloid fluid resuscitation (p = 0.026). Rapid improvement in early acidosis and coagulopathy was superior with an MTP (p = 0.009). More patients in the MTP group also underwent primary abdominal fascial closure during their hospital stay (p = 0.021). This was most evident with grade 4 injuries (89% vs. 14%). The mean time to fascial closure was 4.2 days. The overall survival rate for all major liver injuries was not affected by an MTP (p = 0.61).

Conclusion: The implementation of a formal MTP using high plasma and platelet ratios resulted in a substantial increase in abdominal wall approximation. This occurred concurrently to a decrease in the delivered volume of crystalloid fluid.

Contexte : Les protocoles de transfusion massive (PTM) impliquant des rapports plasma:plaquettes élevés sont de plus en plus populaires pour traiter les patients atteints d'un traumatisme hémorragique. Les chirurgies majeures du foie requièrent souvent le déclenchement de protocoles de transfusion massive et une maîtrise immédiate de l'hémorragie. La littérature actuelle décrit les résultats chez des patients victimes de divers types de traumatismes. Nous avons voulu mesurer les effets d'un PTM sur les patients ayant subi un traumatisme majeur au foie.

Méthodes : Nous avons analysé les dossiers de patients ayant subi des blessures au foie de grade 3, 4 ou 5 qui ont nécessité des transfusions massives de composants sanguins. Nous avons comparé les patients ayant nécessité des transfusions importantes de plasma, de culots globulaires et de plaquettes selon un rapport (1:1:1; 2007–2009) à des patients ayant subi leur traumatisme avant la mise en œuvre d'un PTM par l'établissement (2005–2007).

Résultats : Sur 50 patients ayant subi des lésions hépatiques majeures, 35 (58 %) ont reçu des traitements de réanimation après la mise en place du PTM. Les caractéristiques propres aux patients et à leurs blessures étaient similaires entre les cohortes. L'application du PTM a significativement amélioré les rapports plasma:culots globulaires:plaquettes et réduit l'administration de cristalloïdes à des fins de réanimation liquidienne (p = 0,026). L'amélioration rapide de l'acidose naissante et de la coagulopathie a été meilleure avec le PTM (p = 0,009). Plus de patients du groupe soumis au PTM ont aussi subi une fermeture aponévrotique abdominale primaire durant leur séjour hospitalier (p = 0,021). Cela s'est surtout observé avec les lésions de grade 4 (89 % c. 14 %). Le délai moyen avant la fermeture aponévrotique a été de 4,2 jours. L'application du PTM n'a pas modifié le taux de survie global pour l'ensemble des traumatismes hépatiques majeurs (p = 0,61).

Conclusion : La mise en place d'un PTM officiel reposant sur des rapports plasma et plaquettes élevés a donné lieu à une augmentation substantielle des fermetures de la paroi abdominale. Cela s'est produit en parallèle avec une diminution du volume de cristalloïdes administrés pour la réanimation liquidienne.

Recent excitement surrounding the use of massive transfusion protocols (MTPs) with high plasma and platelet concentrations for injured patients in physiologic extremis is substantial.[1–20] While the effect on overall mortality in the civilian population is still debated,[21–24] massive resuscitations with high plasma:packed red blood cell (RBC) ratios remain promising for addressing the early coagulopathy[25] and acidosis frequently associated with life-threatening injury.[10] Additional benefits of a formal MTP include earlier administration of blood products during the resuscitation phase, improved overall efficiency, decreased total blood product use during a patient's hospital stay and a substantial economic savings.[24]

Concurrent to the initiation of MTP blood component therapy, the concept of damage control resuscitation also incorporates principles of reduced crystalloid delivery, permissive hypotension and immediate operative and/or angiographic hemorrhage control.[1–26] This constellation of techniques is directed at patients who present in physiologic extremis (pH ≤ 7.1, base deficit ≥ 12.5, and/or core temperature ≤ 34°C).[2,10,26,27] Interestingly, these parameters are nearly identical to the risk factors for the development of primary abdominal compartment syndrome (ACS).[28–30] As a result of improved recognition of the ACS phenomenon as well as the widespread application of temporary abdominal closures (silo) as a preventative measure, the incidence of primary ACS has decreased substantially over the past 5 years.[28,29,31] Unfortunately, the resultant "open" abdomen remains fraught with considerable short and long-term morbidity.[31–35] In the best case scenario this includes a poor quality of life and the need for major reconstructive surgery.[32–35]

In addition to its effect on acidosis and coagulopathy, MTPs have also been shown to substantially reduce the volume of crystalloid fluid delivered during the initial resuscitation period.[1,15,17] Uncontrolled/excessive resuscitation is a clear risk factor for the development of ACS as well as a major obstacle to obtaining definitive fascial closure of the abdominal wall (visceral edema).[28–30,32,35,36] As a result, it can be postulated that the incidence of both primary ACS and the open abdomen in severely injured patients may be reduced with the use of a formal 1:1:1 ratio MTP. Anecdotally, this appeared to be particularly evident in patients with high-grade hepatic injuries at our institution. As a result, the primary goal of our study was to identify the effects of a mature MTP on patients with major liver injuries by comparing them to a control group who underwent massive transfusions before initiation of a formalized high plasma protocol.

Methods

The primary study population consisted of all patients with a high grade liver injury (grade 3, 4 or 5), who presented to Grady Memorial Hospital (GMH), after the implementation of a formal MTP (Feb. 1, 2007, to Feb. 1, 2009; Table 1). The hospital is a level 1 trauma centre located in an urban setting. Massive transfusion was defined as transfusion of ≥ 10 units of RBCs in any 24-hour period during a patient's hospital stay. We compared this population with a cohort with high-grade hepatic injuries who also underwent a massive transfusion (≥ 10 units of RBCs) prior to the initiation of the formal MTP (Jan. 1, 2005, to Jan. 31, 2007). The massive transfusion prospective registry, the trauma patient registry and chart reviews supplied all data. Although our institution does not have a formal protocol for management of the open abdomen, individual clinical practice was essentially identical. All management and challenges were also discussed daily at "Morning Report" by the faculty and senior leadership.

The MTP at GMH is initiated for patients who present in physiologic extremis (acidosis, coagulopathy, hypothermia) as a result of high-grade injuries. It is designed to ensure immediate availability of aggressive and early component therapy and is activated with a phone call to the blood bank. This activation is restricted to an attending physician or fellow from the departments of surgery, anesthesia, emergency medicine or critical care. Efforts are made by clinical personnel to obtain and deliver a sample of the patient's blood to the blood bank for blood typing. The blood bank responds to the call for protocol activation by immediately placing 6 units of group O or type-specific RBCs and 6 units of group AB fresh

Table 1. Massive transfusion protocol package contents*

Package	PRBCs	Plasma	Platelets	Cryoprecipitate
Initiation	6 units (UD/TS)	6 units (UD)		
1 (0.5 h)	6 units (UD/TS)	6 units (UD)	1 apheresis§	
2 (1 h)	6 units (UD/TS)	6 units (TS)		20 units
3 (1.5 h)†	6 units (UD/TS)	6 units (TS)	1 apheresis§	
4 (2 h)	6 units (UD/TS)	6 units (TS)		10 units
5 (2.5 h)	6 units (UD/TS)	6 units (TS)	1 apheresis§	
6 (3 h)‡	6 units (UD/TS)	6 units (TS)		10 units

PRBCs = packed red blood cells; TS = type-specific; UD = universal donor.
*PRBCs and plasma can be doubled to 12 units each per cycle by request.
†Recombinant Factor VIIa may be used at attending physician discretion (dose: 3.6 mg, 1 repeat dose as needed in 30 minutes).
‡If MTP is still active, alternate packages identical to packages 5 and 6 until protocol terminated.
§A single apheresis unit of platelets is considered to equal 8–10 standard units.

frozen plasma (FFP) in a cooler as the "initiation package." For this purpose, the blood bank maintains an adequate inventory of thawed plasma products for immediate distribution. The blood bank then continues to prepare predesignated packages of components to be picked up every 30 minutes with a goal ratio of RBC:FFP:platelets of 1:1:1 (Table 1). The blood bank continues to issue group O RBCs, but, owing to limited group AB plasma inventory, will issue ABO type compatible FFP once the patient's blood type is known. If requested, the blood bank is able to double up the protocol to allow for 12 units of RBCs and 12 units of FFP to be delivered every 30 minutes. In addition, if bleeding is uncontrolled, the clinical service can request a 3.6 mg dose of rFVIIa after package 2 (18 units of RBCs), with an identical second dose, if needed, distributed 30 minutes later. The charge nurse in the area of resuscitation is responsible for designating a "runner," who picks up a cooler every 30 minutes from the blood bank, returns used coolers and delivers product to the patient area. In addition to hemorrhage control, the attending physician is responsible for starting and stopping the protocol and for activating rFVIIa use.

The protocol dictates performing coagulation parameters and blood gases at least every other hour to monitor the patient's response to therapy. The blood bank medical director, through the transfusion committee of the hospital, reviews the MTP quality indicators: 90% or higher percentage of MTP cycles in which blood products are available within 30 minutes and delivered to the resuscitation area in a timely manner; 100% of MTPs in which blood typing specimen was received by the blood bank before the second cycle; 5% or less waste of blood products; and 0% incidence of transfusion reactions.

Exclusion criteria for the study were limited to patients who did not undergo a massive transfusion following a high-grade liver injury. Liver injuries were graded using the American Association for the Surgery of Trauma grading system.[37,38]

Statistical analysis

We performed our statistical analyses using Stata version 8.0 (Stata Corp). Normally or near-normally distributed variables are reported as means, and non-normally distributed variables are reported as medians. We compared means using the Student t test and medians using the Mann–Whitney U test. Differences in proportions among categorical data were assessed using the Fisher exact test. We considered results to be significant at $p < 0.05$ for all comparisons.

Results

A total of 35 and 25 patients with major liver injuries underwent a massive RBC transfusion before and after the initiation of a formal (1:1:1) MTP, respectively. For all grades of major hepatic trauma, patient demographics, injury characteristics, mechanisms, initial hemodynamic status and presenting base deficits were similar between the groups (Tables 2–4).

The overall survival rate for all patients with major liver injuries (grades 3, 4, and 5) was not affected by the implementation of a formal MTP (18 of 35 in the MTP group v. 11 of 25 pre-MTP, $p = 0.61$). Most patients in the MTP cohort died of massive exsanguinating hemorrhage and physiologic exhaustion (33% of grade 3, 86% of grade 4, 88% of grade 5 patients). The rate of primary abdominal fascial closure prior to discharge was significantly higher in the patient cohort who received a higher FFP:RBC ratio (12 of 18 in the MTP group v. 3 of 11 in the pre-MTP group, $p = 0.02$). This was a result of the large difference between patients with grade 4 injuries (8 in the MTP group v. 1 in the pre-MTP group; Table 3). Of the 6 patients who did not achieve fascial closure prior to discharge, 5 had prolonged mechanical limitations of the abdominal wall following a massive crystalloid-based resuscitation. The remaining patient required multiple operative interventions for concurrent injuries and displayed moderate intraperitoneal sepsis as a driving factor. Of the 8 patients with grade 4 liver injuries in the MTP

Table 2. Comparison of patients with grade 3 liver injuries after massive transfusion

	Group; mean (%)*	
Variable	MTP	Pre-MTP
Total patients	9	5
Age, median, yr	30	34
Male sex	100	80
Penetrating mechanism	56	80
Injury severity score	31	29
Hemodynamic instability	44	60
Presenting base deficit	–13.3	–16.0
Concurrent injuries	3.3	3.0
Mechanical ventilation, d	16	11
LOS, d	32	38
Overall mortality	3 (33)	3 (60)
Initial damage control procedure	6 (66)	5 (100)
No. of operations among all patients	4	5
Primary abdominal fascial closure	2/6 (33)	1/2 (50)
Achieved by survivors prior to discharge		
PRBC:FFP transfusion	1.28	7.4†
PRBC:platelets transfusion	1.12	17†
Total PRBC units, 24 h	26	28
Total PRBC units, < 6 h	25	24
Crystalloid infusion, L	6	9
Factor VIIa	5 (56)	0
Postoperative INR	1.26	1.98
Postoperative base deficit	–7.1	–9.7

FFP = fresh frozen plasma; INR = international normalized ratio; LOS = length of stay in hospital; MTP = massive transfusion protocol; PRBC = packed red blood cells.
*Unless otherwise indicated.
†$p < 0.05$.

group who underwent successful abdominal fascial closure during their initial hospital stay, 4 were closed during the initial operative procedure and 4 underwent primary fascial approximation at a mean of 4.2 days after admission.

Most patients in the MTP group underwent initial perihepatic packing (66% of grade 3, 47% of grade 4, 73% of grade 5 patients). This was comparable to patients in the pre-MTP group (60% of grade 3, 77% of grade 4, 86% of grade 5 patients; $p = 0.048$).

Discussion

Major hepatic trauma consists of large parenchymal lacerations, hematomas, juxtahepatic venous injuries and complete hepatic avulsions.[37,38] Accordingly, these patients often require substantial transfusions, and high associated mortality correlates with the grade of injury.[37] When operative therapy is required, major liver injuries can also be described as some of the most challenging cases. Because all current massive transfusion literature describes patient morbidity and mortality following generalized injuries, the primary goal of our study was to evaluate the influence of a high plasma ratio MTP on the outcomes of patients with major hepatic trauma.

Injured military and civilian patients classically require massive transfusion of blood products in approximately 8% and 3% of cases, respectively.[39,40] These patients most often present to the hospital in physiologic extremis.[2,15,40] As a result, acidosis was predictably impressive in our patient cohort, with mean base deficits ranging from –13.3 to –16.4, depending on the hepatic grade of injury (Tables 2–4). The severity of their injuries was also evident in the high mean injury severity score (ISS), duration of mechanical ventilation and hospital stay as well as the rate of hemodynamic instability at admission. The observation that 66%–100% of patients required an emergent damage control operative procedure also highlights the extremis in this cohort. When taken as a collective, these patients epitomize the requirement for massive blood product resuscitation and immediate hemorrhage control via damage control principles.

Although there appears to be a clear reduction in mortality for injured soldiers,[10,13–15,41] this finding has recently been questioned within the civilian cohort.[1,21–24] Prior to the implementation of a formalized high plasma MTP (Table 1), mortality for patients who required a massive transfusion (≥ 10 units of RBCs) following grade 3, 4 or 5 hepatic injuries at our institution was 60%, 46% and 71%, respectively. Given associated patient ISS of 31, 26 and 29,

Table 3. Comparison of patients with grade 4 liver injuries after massive transfusion

	Group; mean (%)*	
Variable	MTP	Pre-MTP
Total patients	15	13
Age, median, yr	32	27
Male sex	(93)	(92)
Penetrating mechanism	(73)	(54)
Injury severity score	26	28
Hemodynamic instability	(80)	(77)
Presenting base deficit	–14.6	–14.3
Concurrent injuries	3.7	3.2
Mechanical ventilation, d	14	11
LOS, d	29	25
Overall mortality, no.	6 (40)	6 (46)
Initial damage control procedure, no.	13 (87)	13 (100)
No. of operations among all patients	4	6
Primary abdominal fascial closure	8/9 (89)	1/7 (14)
Achieved by survivors prior to discharge		
PRBC:FFP transfusion	1.56	10.9†
PRBC:platelets transfusion	1.23	16*
Total PRBC units, 24 h	31	24
Total PRBC units, < 6 h	28	20
Crystalloid infusion, L	6	13†
Factor VIIa	6 (40)	2 (15)
Postoperative INR	1.19	1.99
Postoperative base deficit	–4.9	–10.6†

FFP = fresh frozen plasma; INR = international normalized ratio; LOS = length of stay in hospital; MTP = massive transfusion protocol; PRBC = packed red blood cells.
*Unless otherwise indicated.
†$p < 0.05$.

Table 4. Comparison of patients with grade 5 liver injuries after massive transfusion

	Group; mean (%)*	
Variable	MTP	Pre-MTP
Total patients	11	7
Age, yr median	29	30
Male sex	(82)	(86)
Penetrating mechanism	(64)	(71)
Injury severity score	29	26
Hemodynamic instability	(91)	(71)
Presenting base deficit	–15.2	–16.4
Concurrent injuries	2.9	2.7
Mechanical ventilation, d	3	4
LOS, d	15	10
Overall mortality, no.	8 (73)	5 (71)
Initial damage control procedure, no.	9 (82)	7 (100)
No. of operations among all patients	1	2
Primary abdominal fascial closure	2/3 (67)	1/2 (50)
Achieved by survivors prior to discharge		
PRBC:FFP transfusion	1.65	6.1†
PRBC:platelets transfusion	2.03	3.8
Total PRBC units, 24 h	23	37†
Total PRBC units, < 6 h	17	29†
Crystalloid infusion, L	6	11†
Factor VIIa	2 (18)	2 (29)
Postoperative INR	1.31	1.49
Postoperative base deficit	–13.4	–14.6

FFP = fresh frozen plasma; INR = international normalized ratio; LOS = length of stay in hospital; MTP = massive transfusion protocols; PRBC = packed red blood cells.
*Unless otherwise indicated.
†$p < 0.05$.

respectively, as well as at least 3 concurrent injuries among all cohorts, these survival ratios appear appropriate (Tables 2–4). Unfortunately, mortality in this patient cohort remained unchanged after the implementation of a high plasma ratio MTP (33%, 47%, 73%, respectively). This observation was surprising, given the previous identification of an improved overall survival among blunt trauma patients who received an MTP resuscitation at our trauma centre.[42] Considering the strikingly similar mortality between the pre- and post-MTP cohorts for grade 4 and 5 liver injuries, however, we believe this is unlikely to be the result of sample size bias. This lack of reduction in mortality despite the 1:1:1 massive transfusion has been previously described in mixed cohorts of injured patients.[21,24] It remains consistent when the mortality bias is corrected,[23] despite a clear improvement in early coagulopathy.[22] This area of debate is likely to continue until a prospective randomized trial is completed.[1,4–7,9]

Although the technique of perihepatic packing was founded in 1908 with Pringle's discussion of hepatic trauma,[43] the modern interpretation of this work occurred in the late 1970s,[44–46] followed by the concept of truncated operations with concurrent intra-abdominal packing for patients in physiologic extremis by Stone and colleagues in 1983.[47] This philosophy was then coined "damage control" by Rotondo and colleagues, given its obvious conceptual similarity to the Navy's use of the same term.[48,49] Although this concept has resulted in a substantial improvement in mortality when applied to the correct patient population,[49] it also commits the patient to a series of subsequent operative procedures aimed at restoring gastrointestinal continuity and abdominal wall closure.[26] Unfortunately, many patients are eventually left with "open" abdomens because of generalized visceral edema caused by their initial resuscitation and the prevention of ACS. Although these abdomens are covered by a skin graft, the short and long-term morbidity, economic and resource cost are substantial and mortality is high.[32–35,50]

The abdominal wall closure rate associated with the implementation of a 1:1:1 MTP was higher than in patients who received a low plasma massive transfusion (67% v. 27%) despite the use of similar intraoperative techniques. While these rates did not vary in patients with either grade 3 or 5 liver trauma, a large improvement was noted in patients with grade 4 injuries (14% v. 89%; Table 3). The observed decrease in crystalloid resuscitation following the use of an MTP in patients with grade 4 injuries (13 v. 6 L) was also striking. This supports the anecdotal observation that generalized visceral edema is reduced when plasma and blood products are delivered via a crystalloid sparing MTP.[1,15,17] To this end, 4 patients with grade 4 trauma even underwent immediate fascial closure during the initial operative procedure. This compares to a mean wait of 4.2 days in the remaining patients who had successful approximation of their abdominal wall during the initial hospital stay. We believe this decrease in both visceral and abdominal wall edema played an important role in achieving higher rates of definitive abdominal fascial closure. The 54% reduction to 6 L of administered crystalloids is also interesting, given that the published threshold for increasing the risk for ACS is 7.5 L.[28–30,32,35] The same statistical decrease in crystalloid resuscitation was not observed in patients with grade 3 injuries, who failed to show an increase in closure rates despite implementation of the formal MTP (Table 2). This potential link has recently been suggested elsewhere.[1] Unfortunately, most patients with grade 5 hepatic injuries died of exsanguinating hemorrhage (Table 4), likely obscuring any potential improvement in abdominal closure associated with a crystalloid sparing MTP.

As an MTP quality control measure, we also evaluated the actual RBC:FFP ratios delivered to each patient. For those with grade 3 liver injuries, the mean RBC:FFP ratios improved from 7.4 to 1.28 with the implementation of a formal MTP (Table 2). This pattern was also observed in patients with grade 4 (from 10.9 to 1.56; Table 3) and grade 5 (from 6.1 to 1.65; Table 4) injuries; RBC:platelet ratios also improved. Furthermore, the utility of the MTP was particularly evident in the correction of acidosis among patients with grade 4 injuries (–10.6 to –4.9).

Limitations

Limitations in this study are multiple. First, it was retrospective; therefore, the possibility of bias cannot be eliminated. Second, although mortality among patients with grade 4 and 5 liver injuries pre- and post-MTP were nearly identical, our study was substantially underpowered to assess overall mortality. While our primary goal was to descriptively evaluate the impact of an MTP on major liver injuries, small sample size (grade 3 injuries) may have obscured improvements in mortality. Finally, although an increased abdominal fascial closure rate was evident, observed decreases in visceral and abdominal wall edema were anecdotal. As a result, confirmatory abdominal wall measurements and intra-abdominal pressures would be helpful in future studies.

Conclusion

The implementation of a formal MTP using high plasma and platelet ratios resulted in a substantial increase in abdominal wall approximation. This occurred concurrently to a decrease in the volume of crystalloid fluid delivered during the initial resuscitation for massive hemorrhage. We hypothesize that this improvement was related to an overall decrease in generalized edema of both the viscera and abdominal wall. It was particularly pronounced in patients with grade 4 injuries. Given the rapid adoption and initiation of modern 1:1:1 MTPs across the globe,[3] the targeted effects of this strategy among civilians with specific organ injuries should be further defined prospectively.

Competing interests: D.V. Feliciano declares having received speaker fees. No other competing interests declared.

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